Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Shaw AT, Kim D-W, Mehra R, et al. Ceritinib in *ALK*-rearranged non–small-cell lung cancer. N Engl J Med 2014;370:1189-97. DOI: 10.1056/NEJMoa1311107

SUPPLEMENTARY APPENDIX

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Dose Recommendation Guidelines and Maximum Tolerated Dose Determination

Dose Recommendation Guidelines

For the purpose of dose-escalation decisions, only dose limiting toxicities (DLTs) occurring during the first cycle of treatment, including the PK run-in period, were considered in the Bayesian logistic regression model (BLRM).

After each cohort of patients the posterior distributions for the probabilities of DLT rates at different dose levels were obtained. The results of this analysis were summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level had of lying in each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1.00] excessive toxicity.

Following the principle of escalation with overdose control (EWOC), after each cohort of patients the recommended dose is the one with the highest posterior probability of the DLT rate falling in the target interval [16%, 33%) among the doses fulfilling EWOC, i.e. it is unlikely (<25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval. Based on this approach, multiple cohorts might be enrolled to the same dose level. After completion of a given cohort, the decision to dose escalate, de-escalate or remain at the same dose, and the actual dose chosen depends on this calculation of risk assessment using the BLRM and medical review of available clinical and laboratory data.

For further understanding of the safety, tolerability and pharmacokinetics (PK) of ceritinib, additional cohorts of patients were enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation. These additional cohorts were referred to as enrichment cohorts.

Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the maximum tolerated dose (MTD), but it may not be an admissible dose according to the overdose criterion. Since vague prior information was used for the probabilities of DLT, in the early stages of the study this escalation procedure reflected a conservative strategy.

The dose recommended by the adaptive BLRM was to be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated. However, the next dose level could not exceed the dose recommended by the BLRM in conjunction with protocol specified restrictions on dose increments. Full details of the criteria for dose escalation and the determination of the MTD are provided in Section 5.1.2.4 of the protocol.

Posterior probabilities of toxicity at the MTD

The starting dose of ceritinib was 50 mg QD in a 21-day cycle plus PK run-in period. Additional cohorts of patients received treatment with escalation and enrichment doses of ceritinib until the MTD/Recommended Dose for Expansion (RDE) was reached at 750 mg QD. In total, 59 patients were treated during the dose escalation phase, with 54 patients evaluable for determining the MTD per protocol definition (Section 5.1.2.4 of the protocol). See Table S3 for a summary of patients treated in the dose escalation by dose level.

Based on the Cycle 1 DLT data for the 54 evaluable patients at the time of MTD determination, the posterior probabilities of toxicity are summarized in Table S1. The dose levels shaded in gray represent dose levels that violated the overdose criteria, that is, values in column “P (Excessive) 0.33–1” greater than 0.25. Hence they have a greater than 25% chance of being excessively toxic. Based on the BLRM recommendation alone, the dose could have been escalated to 900 mg. However, discussion at the Dose Escalation Teleconference between study investigators and Novartis concluded that in light of the high frequency of persistent low-grade nausea, vomiting and diarrhea seen with ceritinib, and the occasional occurrence of higher grade gastrointestinal toxicities and transaminase elevations in later cycles, it was clinically most appropriate not to escalate the dose beyond 750 mg. The investigators and Novartis agreed that the MTD was 750 mg QD. The dose of ceritinib at 750 mg (highlighted in bold in Table S1) was selected as the recommended dose for phase I expansion. At 750 mg, the probability of being in the target toxicity interval is 54.2%, while the probability of being in the excessive toxicity interval is only 3.3%.

Figure S1. Pharmacokinetics of Ceritinib During the 3-Day Pharmacokinetic Run-in Period, and Cycle 1 Day 8.

A.

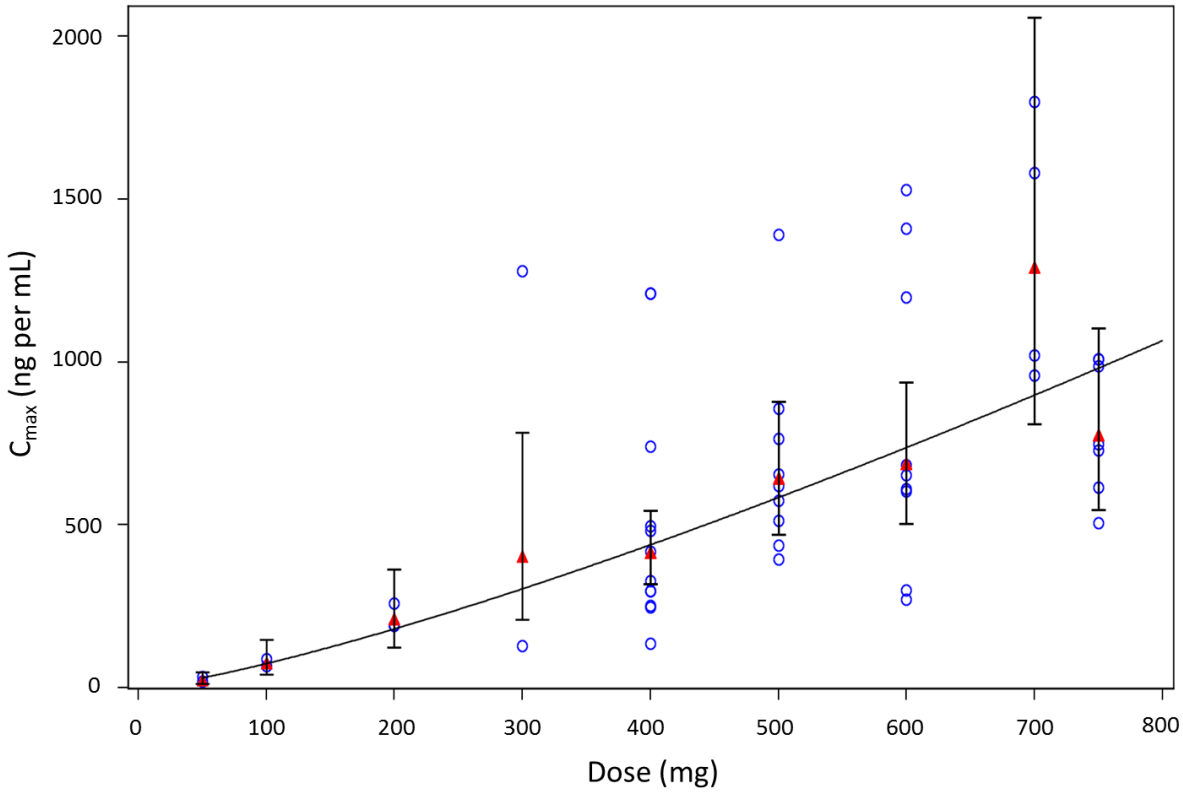


Figure S1A. C_{max} of ceritinib after multiple daily oral doses on cycle 1 day 8 across the dose range from 50 to 750 mg. The model $\ln(C_{max}) = \alpha + \beta \ln(\text{dose})$ was used to assess the dose proportionality of ceritinib. The solid line represents the model estimated regression line; blue open circles represent individual values, red filled triangles represent the least square mean and vertical lines represent the 90% confidence interval of least square mean.

B.

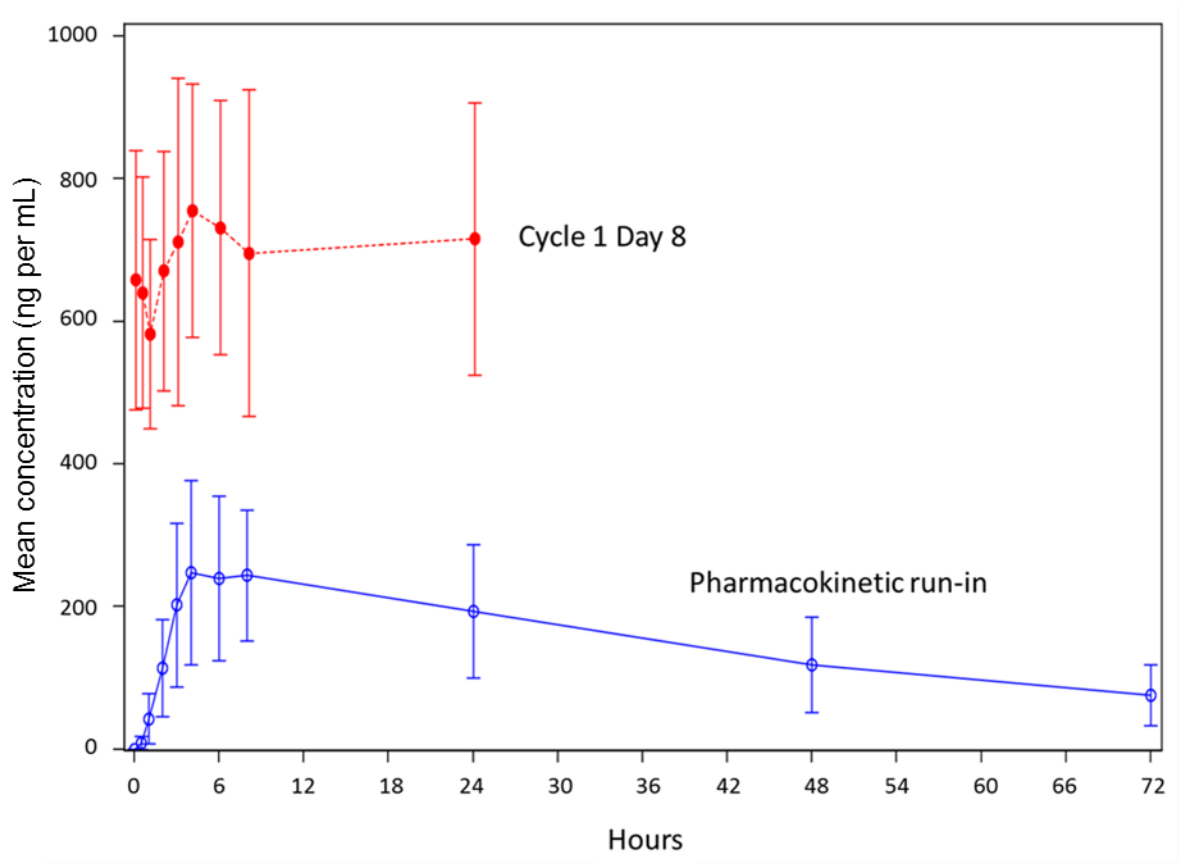
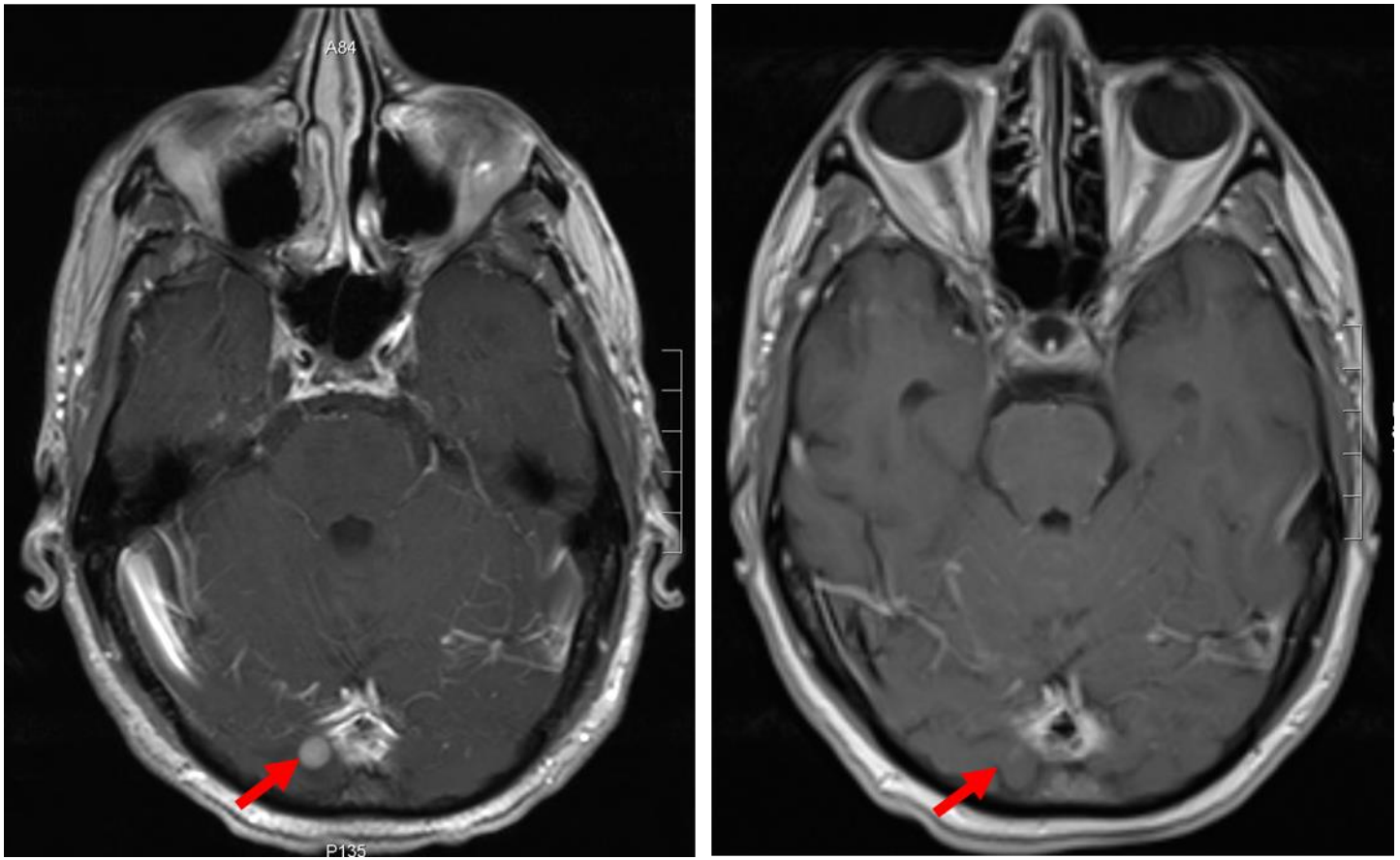


Figure S1B. Mean plasma concentration–time profiles of ceritinib after the first oral dose on day 1 of the 3-day pharmacokinetic run-in period, and after multiple daily oral doses on cycle 1 day 8, at the maximum tolerated dose of 750 mg per day. Error bars represent standard deviation.

Figure S2. Central Nervous System Metastasis and Response to Ceritinib



Shown are magnetic resonance imaging scans of the brain from a patient with crizotinib-resistant disease. This patient had a new, untreated, asymptomatic brain metastasis at the time of study enrolment (left). Repeat brain imaging obtained after 7 weeks of ceritinib demonstrated reduction in the size of the brain lesion (right). Shown are post gadolinium, T1-weighted, axial images. Although the images are not precisely aligned due to patient positioning, the scan performed during ceritinib therapy shows no evidence of enhancement on adjacent inferior and superior cuts.

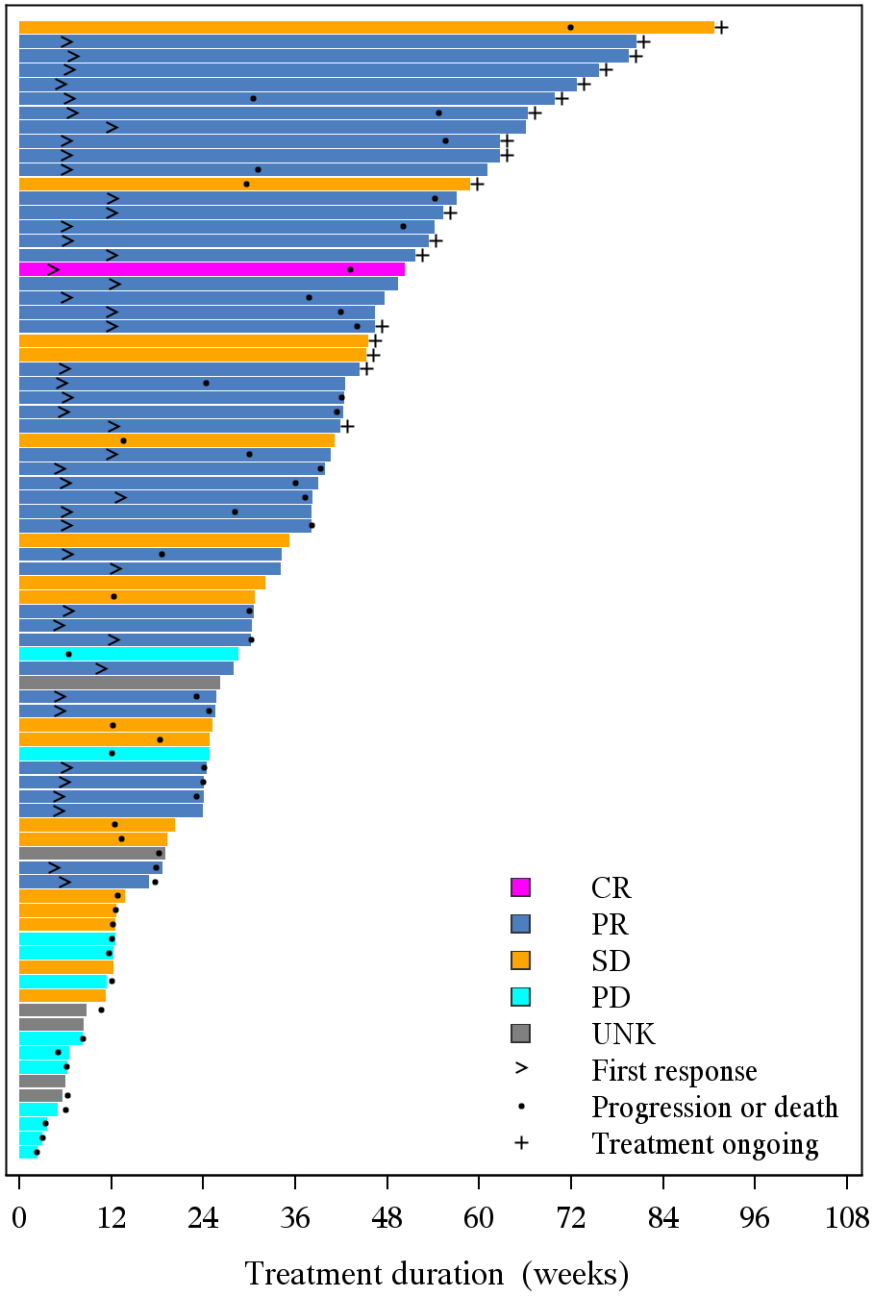


Figure S3. Duration of Treatment With Ceritinib.

Figure S3A (left). Duration on ceritinib ≥400 mg per day for crizotinib-pretreated patients with NSCLC.

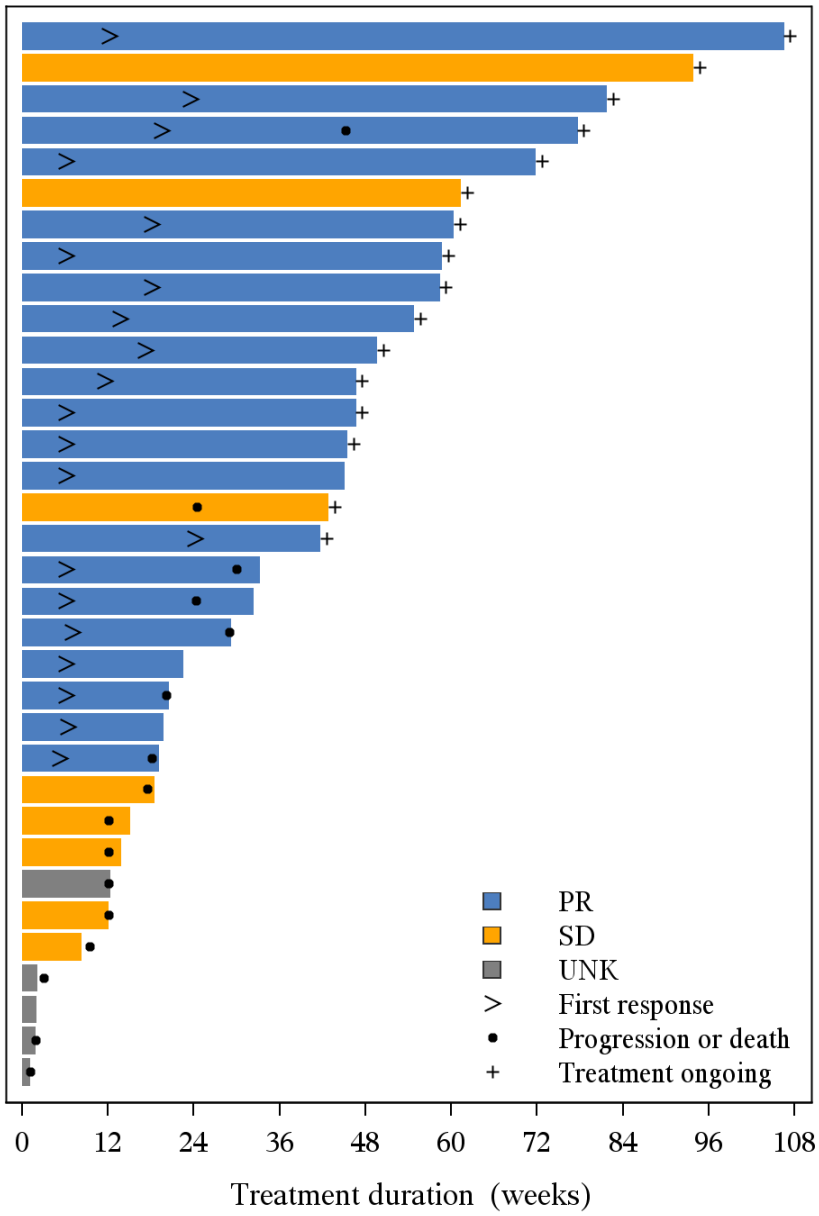


Figure S3B (left). Duration on ceritinib ≥400 mg per day for crizotinib-naive patients with NSCLC.

Table S1. Posterior Summary Information of Dose limiting Toxicity for Different Doses of Ceritinib at the Maximum Tolerated Dose.

Ceritinib Dose – mg per day	P (Under) 0–0.16	P (Target) 0.16–0.33	P (Excessive) 0.33–1	Mean	SD	2.5 %	50 %	97.5 %
50	1	0	0	0.012	0.016	0	0.006	0.057
100	1	0	0	0.021	0.022	0	0.014	0.079
200	0.998	0.002	0	0.039	0.029	0.003	0.033	0.112
300	0.989	0.011	0	0.06	0.035	0.01	0.055	0.142
400	0.958	0.041	0	0.084	0.039	0.024	0.078	0.172
500	0.874	0.126	0	0.109	0.043	0.04	0.104	0.207
600	0.702	0.297	0.001	0.137	0.051	0.054	0.132	0.25
650	0.599	0.396	0.004	0.152	0.056	0.06	0.146	0.277
700	0.505	0.482	0.013	0.167	0.063	0.065	0.159	0.308
750	**0.425**	**0.542**	**0.033**	**0.182**	**0.07**	**0.07**	**0.173**	**0.343**
900	0.262	0.601	0.136	0.227	0.097	0.083	0.211	0.461
1050	0.179	0.561	0.26	0.27	0.123	0.094	0.247	0.576

SD, Standard deviation.

Table S2. Prior Antineoplastic Therapy (>10% of Patients with NSCLC).*

Prior Therapeutic Medication (Class and/or Preferred Term)	NSCLC Patients N=122
Any	122 (100)
Platinums	107 (88)
Carboplatin	61 (50)
Cisplatin	65 (53)
Oxaliplatin	1 (1)
Pemetrexed†	94 (77)
Crizotinib	83 (68)
Taxanes	54 (44)
Docetaxel	27 (22)
Paclitaxel	33 (27)
Bevacizumab	31 (25)
Gemcitabine†	28 (23)
Erlotinib†	27 (22)
Vinorelbine†	21 (17)

*Therapeutic agents are listed here if they were received by 10% or more of patients.
†Including salt formulations.

Table S3. Patients Treated in Dose Escalation by Dose, and Dose-limiting Toxicities of Ceritinib Occurring During the First Cycle of Treatment.*

Dose — mg per day	Patients — no. N = 59*	Dose-limiting Toxicity†	Study Treatment
50	2	–	–
100	2	–	–
200	3	–	–
300	3	–	–
400	14	Grade 3 elevated transaminases and grade 2 elevated ALT	Held, resumed at 200 mg
		Grade 3 hypophosphatemia	Continued at same dose
500	10	–	–
600	10	Grade 3 diarrhea	Held, resumed at 400 mg
		Grade 3 dehydration	Off study for simultaneous disease progression
700	5	–	–
750	10	Grade 3 diarrhea and grade 3 vomiting	Held, resumed at 500 mg, held for nausea, resumed at 400 mg
		Intolerable grade 2 diarrhea	Held, resumed at 600 mg

*Determination of the maximum tolerated dose was based on 54 patients evaluable per protocol for the dose escalation; among the treated patients above, 1 at 100 mg, 2 at 500 mg, and 2 at 750 mg were not evaluable for the dose determining set.

†Dose-limiting toxicities were defined as clinically relevant adverse events or abnormal laboratory values meeting pre-specified criteria, and assessed as unrelated to disease progression, concurrent illness, or concomitant medications.

Table S4. Adverse Events of Any Grade, Regardless of Study Drug Relationship, in ≥ 5% of Patients Treated with Ceritinib.*

Adverse Event (Preferred Term)	Dose Level — mg per day									
	50	**100**	**200**	**300**	**400**	**500**	**600**	**700**	**750**	**Total**
	n=2	**n=2**	**n=3**	**n = 3**	**n = 14**	**n = 10**	**n = 10**	**n = 5**	**n = 81**	**N = 130**
	no. of patients (%)									
Patients with any adverse event	2 (100)	2 (100)	3 (100)	3 (100)	14 (100)	10 (100)	10 (100)	5 (100)	81 (100)	**130 (100)**
Nausea	0	1 (50)	2 (67)	2 (67)	10 (71)	9 (90)	10 (100)	5 (100)	67 (83)	**106 (82)**
Diarrhea	0	0	2 (67)	1 (33)	9 (64)	7 (70)	8 (80)	4 (80)	67 (83)	**98 (75)**
Vomiting	0	1 (50)	3 (100)	1 (33)	8 (57)	6 (60)	8 (80)	4 (80)	53 (65)	**84 (65)**
Fatigue	1 (50)	1 (50)	1 (33)	0	5 (36)	4 (40)	8 (80)	0	41 (51)	**61 (47)**
Elevated alanine aminotransferase levels	0	0	1 (33)	0	2 (14)	3 (30)	2 (20)	4 (80)	33 (41)	**45 (35)**
Constipation	0	0	1 (33)	0	3 (21)	3 (30)	4 (40)	2 (40)	29 (36)	**42 (32)**
Abdominal pain	0	0	1 (33)	1 (33)	1 (7)	2 (20)	2 (20)	1 (20)	31 (38)	**39 (30)**
Decreased appetite	0	1 (50)	1 (33)	0	0	3 (30)	4 (40)	3 (60)	26 (32)	**38 (29)**
Elevated aspartate aminotransferase levels	0	0	1 (33)	0	3 (21)	2 (20)	2 (20)	3 (60)	22 (27)	**33 (25)**
Cough	0	0	2 (67)	0	3 (21)	3 (30)	2 (20)	0	20 (25)	**30 (23)**
Asthenia	0	1 (50)	1 (33)	1 (33)	2 (14)	1 (10)	3 (30)	3 (60)	16 (20)	**28 (22)**
Weight decreased	0	0	1 (33)	0			0	3 (60)	16 (20)	**26 (20)**
Dyspnea	2 (100)	0	1 (33)	1 (33)	2 (14)	4 (40)	0	0	12 (15)	**22 (17)**

Headache	1 (50)	0	1 (33)	0	2 (14)	0	3 (30)	1 (20)	12 (15)	**20 (15)**
Pyrexia	0	0	1 (33)	0	0	1 (10)	1 (10)	1 (20)	16 (20)	**20 (15)**
Back pain	0	0	1 (33)	1 (33)	3 (21)	1 (10)	2 (20)	1 (20)	10 (12)	**19 (15)**
Elevated blood alkaline phosphatase levels	0	0	0	0	1 (7)	0	2 (20)	1 (20)	15 (19)	**19 (15)**
Hypokalemia	0	0	1 (33)	0	2 (14)	1 (10)	0	1 (20)	14 (17)	**19 (15)**
Anemia	0	0	0	1 (33)	2 (14)	2 (20)	3 (30)	0	9 (11)	**17 (13)**
Insomnia	0	0	0	0	1 (7)	3 (30)	0	1 (20)	12 (15)	**17 (13)**
Musculoskeletal pain	0	0	1 (33)	0	2 (14)	2 (20)	2 (20)	1 (20)	9 (11)	**17 (13)**
Dyspepsia	1 (50)	0	0	0	0	2 (20)	3 (30)	1 (20)	9 (11)	**16 (12)**
Musculoskeletal chest pain	0	0	0	0	0	0	1 (10)	0	14 (17)	**15 (12)**
Arthralgia	0	0	0	0	2 (14)	1 (10)	0	1 (20)	10 (12)	**14 (11)**
Increased blood creatinine	0	0	0	0	1 (7)	1 (10)	0	0	12 (15)	**14 (11)**
Dizziness	0	0	0	0	2 (14)	1 (10)	0	0	11 (14)	**14 (11)**
Hypophosphatemia	0	0	0	0	1 (7)	1 (10)	2 (20)	0	9 (11)	**13 (10)**
Pain in extremity	0	0	0	1 (33)	0	1 (10)	1 (10)	1 (20)	9 (11)	**13 (10)**
Upper respiratory tract infection	0	0	1 (33)	0	3 (21)	2 (20)	1 (10)	0	6 (7)	**13 (10)**
Abdominal pain upper	0	0	0	0	2 (14)	0	0	1 (20)	9 (11)	**12 (9)**
Rash	0	0	1 (33)	0	1 (7)	1 (10)	1 (10)	0	8 (10)	**12 (9)**
Hypomagnesemia	0	0	1 (33)	0	1 (7)	1 (10)	2 (20)	0	6 (7)	**11 (8)**

Muscle spasms	1 (50)	0	0	0	0	0	1 (10)	1 (20)	8 (10)	**11 (8)**
Non-cardiac chest pain	0	0	0	0	0	0	1 (10)	0	10 (12)	**11 (8)**
Oropharyngeal pain	0	0	1 (33)	0	0	1 (10)	2 (20)	2 (40)	5 (6)	**11 (8)**
Increased amylase	0	0	0	0	0	0	3 (30)	0	7 (9)	**10 (8)**
Increased lipase	0	0	0	1 (33)	0	0	1 (10)	0	8 (10)	**10 (8)**
Peripheral edema	0	0	0	0	1 (7)	1 (10)	0	1 (20)	7 (9)	**10 (8)**
Pneumonia	0	0	0	0	0	0	0	1 (20)	9 (11)	**10 (8)**
Pruritis	0	0	1 (33)	0	0	1 (10)	1 (10)	0	7 (9)	**10 (8)**
Stomatitis	0	0	0	0	1 (7)	0	0	0	9 (11)	**10 (8)**
Anxiety	0	0	1 (33)	0	0	0	0	0	8 10)	**9 (7)**
Chills	0	0	0	0	1 (7)	0	0	0	8 (10)	**9 (7)**
Depression	0	0	0	0	1 (7)	0	0	0	8 (10)	**9 (7)**
Dysphonia	0	0	0	0	0	0	0	1 (20)	8 (10)	**9 (7)**
Hyperglycemia	0	0	0	0	0	0	1 (10)	0	8 (10)	**9 (7)**
Tremor	0	0	0	0	0	0	0	0	9 (11)	**9 (7)**
Urinary tract infection	0	0	0	0	0	0	2 (20)	0	7 (9)	**9 (7)**
Convulsion	0	0	0	0	1 (7)	0	1 (10)	0	6 (7)	**8 (6)**
Dry skin	0	0	0	0	1 (7)	0	1 (10)	0	6 (7)	**8 (6)**
Dysgeusia	0	0	1 (33)	0	0	1 (10)	0	1 (20)	5 (6)	**8 (6)**

QTc prolongation	0	0	0	0	0	0	2 (20)	1 (20)	5 (6)	**8 (6)**
Hyponatremia	0	0	0	0	1 (7)	1 (10)	2 (20)	0	4 (5)	**8 (6)**
Dehydration	0	0	0	0	1 (7)	0	1 (10)	0	5 (6)	**7 (5)**
Exertional dyspnea	0	0	0	0	0	2 (20)	0	0	5 (6)	**7 (5)**
Gastroesophageal reflux disease	0	0	0	0	0	1 (10)	1 (10)	0	5 (6)	**7 (5)**
Neck pain	0	1 (50)	0	0	0	0	0	0	6 (7)	**7 (5)**
Pain	1 (50)	0	1 (33)	0	0	1 (10)	1 (10)	0	3 (4)	**7 (5)**

*Patients who experienced more than one occurrence of the same event are only counted once within each category. Patients are categorized according to initial dose received.

Table S5. Response Rate in Patients with *ALK*-Positive NSCLC Treated with Ceritinib ≥400 and 750 mg per day (Investigator-Assessed Responses Confirmed per RECIST 1.0).

Response to Ceritinib ≥400 mg per day	**All NSCLC N = 114**	**NSCLC Crizotinib-pretreated N = 80**	**NSCLC Crizotinib-naive N = 34**
Type of response — no. (%)			
Complete response	1 (1)	1 (1)	0
Partial response	65 (57)	44 (55)	21 (62)
Stable disease	25 (22)	17 (21)	8 (24)
Progressive disease	12 (11)	12 (15)	0
Unknown response*	11 (10)	6 (8)	5 (15)
Overall response rate† — no. (%)	66 (58)	45 (56)	21 (62)
95% CI	48–67	45–67	44–78

Response to Ceritinib 750 mg per day	**All NSCLC N = 78**	**NSCLC Crizotinib-pretreated N = 50**	**NSCLC Crizotinib-naive N = 28**
Type of response — no. (%)			
Complete response	0	0	0
Partial response	46 (59)	28 (56)	18 (64)
Stable disease	14 (18)	8 (16)	6 (21)
Progressive disease	8 (10)	8 (16)	0
Unknown response*	10 (13)	6 (12)	4 (14)
Overall response rate† — no. (%)	46 (59)	28 (56)	18 (64)
95% CI	47–70	41–70	44–81

*Response unknown due to early discontinuation from study.

†Complete responses plus partial responses.

Table S6. Summary of Non-NSCLC Patients Treated with Ceritinib.

Cancer Type	Diagnostic Testing	Ceritinib Dose (mg per day)	Best Response	DOR (months)	PFS (months)
Alveolar rhabdomyosarcoma	FISH	100	PD	–	0.63
Breast cancer	FISH	200	UNK	–	1.5
Breast cancer	FISH	400	UNK	–	0*
Breast cancer	FISH	400	PD	–	2.2
Breast cancer	FISH	600	UNK	–	1.5
Anaplastic large-cell lymphoma	IHC/FISH	750	PR	9.5*	12.3*
Rectal adenocarcinoma	RT-PCR	750	PD	–	2.0
Inflammatory myofibroblastic tumor	IHC	750	PR	9.7*	11.1*

* Censored for DOR or PFS

DOR, duration of response; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PD, progressive disease; PFS, progression-free survival; PR, partial response; RT-PCR, reverse transcription polymerase chain reaction; UNK, unknown.